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Recent Development of Synthetic Strategies Towards the Synthesis of Azomethine Analogues: A Brief Review

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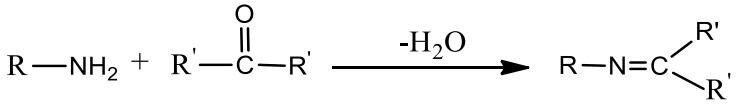
Abstract: The present review outlines the synthetic routes for forming azomethines and also emphasizes the applications of azomethines in various fields. Azomethines holds a prominent and great potential in synthetic organic chemistry due to their unique structural feature. Azomethines are condensation products of Primary amines and a carbonyl compound. In the present scenario, they are attaining significance because of their vast range of applications in the material science and biological field.

Keywords: azomethine, synthesis, current trends, reagents, solvents, catalyst

1. Introduction

The main aims of green chemistry are to carry out reactions and synthetic procedures with energy efficiency and low cost and use those that are safe for human health and the environment. These aims can be fulfilled by redesigning the academic and industrial synthetic processes. Some other strategies in green chemistry are reducing waste generation, using recyclable catalysts and reagents, employing clean energy sources, cutting down accidents rate, preparing reusable and greener products, using defensible raw materials, and making nontoxic chemicals and solvents. Therefore, a scientist will find greener procedures in terms of chemicals, solvents, catalysts, energy sources, and synthetic separation and purification processes from the viewpoint of green chemistry instead of conventional processes [1].

Azomethines, known as Schiff bases, constitute one of the most important classes of bioactive heterocycles. These were first discovered by Hugo Schiff in 1864 and hence named so after the name of the inventor. These are the compounds containing imine(-CH=N-) linkage. These are generally formed by condensing primary amines and carbonyl compounds [2].



Scheme 1. Preparation of azomethines.

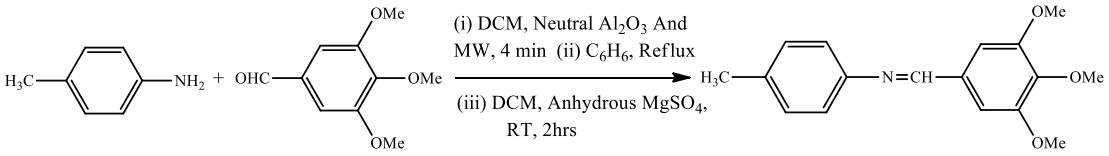
Azomethines have drawn significant attention from researchers because of their wide range of applications in various fields of chemistry. Azomethines have been proven to be

excellent complexing agents [3-9]. They also exhibit many pharmacological activities like antibacterial, antifungal, anti-inflammatory, analgesic, antihelmintic, anticancer, antifertility, antihypertensive, anticonvulsant, anti-HIV, antitumor, antimicrobial, antidepressant, anti-dyslipidemia, antiparasitic, antiproliferative, antitubercular, herbicidal and insecticidal [10-28]. They also serve as very good intermediates in a number of synthetic processes [29]. Applications of azomethines are also reflected in magnetic chemistry, photophysical processes, nonlinear optics, catalysis, chemical analysis, absorption, and transport of oxygen [30]. Azomethines are also applied as corrosion inhibitors as they suppress corrosion by quickly forming a single layer on the surface to be protected [31]. Currently, azomethines are applied for designing versatile chemo/biosensors and as cytoplasm staining dyes [32,33].

2. Different Reaction Conditions for the Formation of Azomethine.

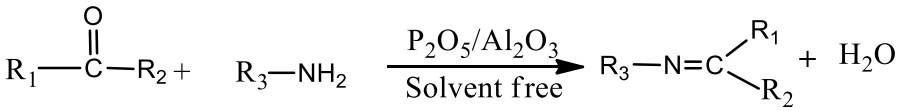
Several synthetic protocols for the formation of azomethines are reported in the literature. Many of these procedures involve using toxic, harmful, and nonbiodegradable catalysts and solvents. These catalysts and solvents are unsafe for the environment and humankind; hence, researchers have developed several environmentally benign methods involving green catalysts and solvents to prepare azomethines to keep the environment clean and green and conserve energy resources. This review describes the synthetic routes for the formation of azomethines. These synthetic routes are described below:

Zhaoqi Y *et al*. [34] reported the synthesis of azomethine with the use of 3,4,5-trimethoxybenzaldehyde and p-toluidine by applying different conditions (a) MW, neutral alumina, and dichloromethane (b) reflux, benzene (c) stirring at RT with DCM, anhydrous $MgSO_4$. They compared all three methods and found the best microwave-assisted method as the yield obtained was maximum and the time taken was minimum.



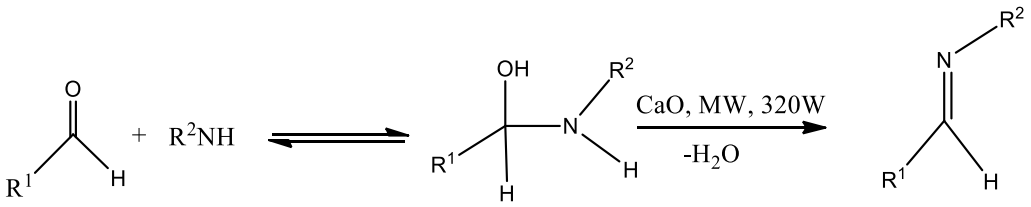
Scheme 2. Synthesis of azomethines by Zhaoqi Y *et al*.

In 2006 novel and highly efficient synthesis of Schiff bases by carrying out a reaction between carbonyl compounds and primary amines under solvent-free conditions in the presence of catalyst P_2O_5/ Al_2O_3 was reported by Naeimi H *et al*. [35]. Schiff bases obtained by them were characterized by IR and ^{1}H-nmr. The method was highly advantageous because azomethines were produced in excellent yield and in a short duration of time.



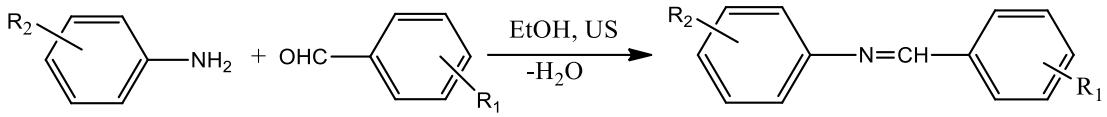
Scheme 3. P_2O_5/ Al_2O_3 catalyzed synthesis of azomethines by Naeimi H *et al*.

Gopalakrishnan *et al*. [36] described the microwave-assisted synthesis of azomethines catalyzed by CaO in 2007. They performed reactions with a variety of aromatic aldehydes and aromatic amines in the presence as well as in the absence of a catalyst. Gopalakrishnan *et al*. also carried out reactions at different temperatures in the presence of a catalyst. Finally, they sum up that with CaO under MW irradiations highest amount of azomethines was obtained in a very short duration of time.



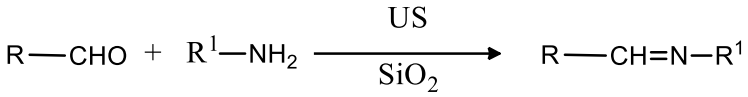
Scheme 4. Synthesis of azomethines by Gopalakrishnan *et al*.

Synthesis of Schiff bases under ultrasound irradiations in the presence of ethanol solvent was reported by Yu Yuye [37] in 2007. To determine the effect of substituents, many azomethines were prepared with electron-rich and electron-deficient aldehydes and with electron-poor and electron-rich anilines. They noticed that the reaction rate increased when it was performed with electron-deficient aldehydes and electron-rich anilines. All the reactions carried out by them were completed in 10-20 min.



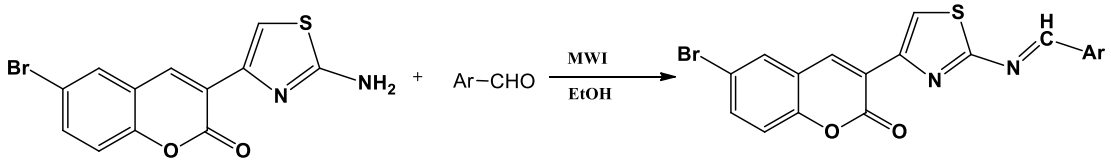
Scheme 5. US-assisted synthesis of azomethines by Yu Yuye *et al*.

The Ecofriendly synthesis of imines by the application of ultrasound irradiation was reported by Stefani HA *et al*. [38] in the year 2007. They prepared a series of azomethine by condensing primary amines and aldehydes using silica as the promoter. They also did the screening of a wide variety of promoters to the imine formation by carrying out the standard reaction of benzaldehyde and p-methoxyaniline in ethanol under ultrasound conditions. Still, the maximum yield was obtained with silica that's why it was chosen as a promoter to carry out other reactions by the researchers. All the azomethines were obtained in excellent yield by the scientists.



Scheme 6. SiO_2 promoted synthesis of azomethines by Patil *et al*.

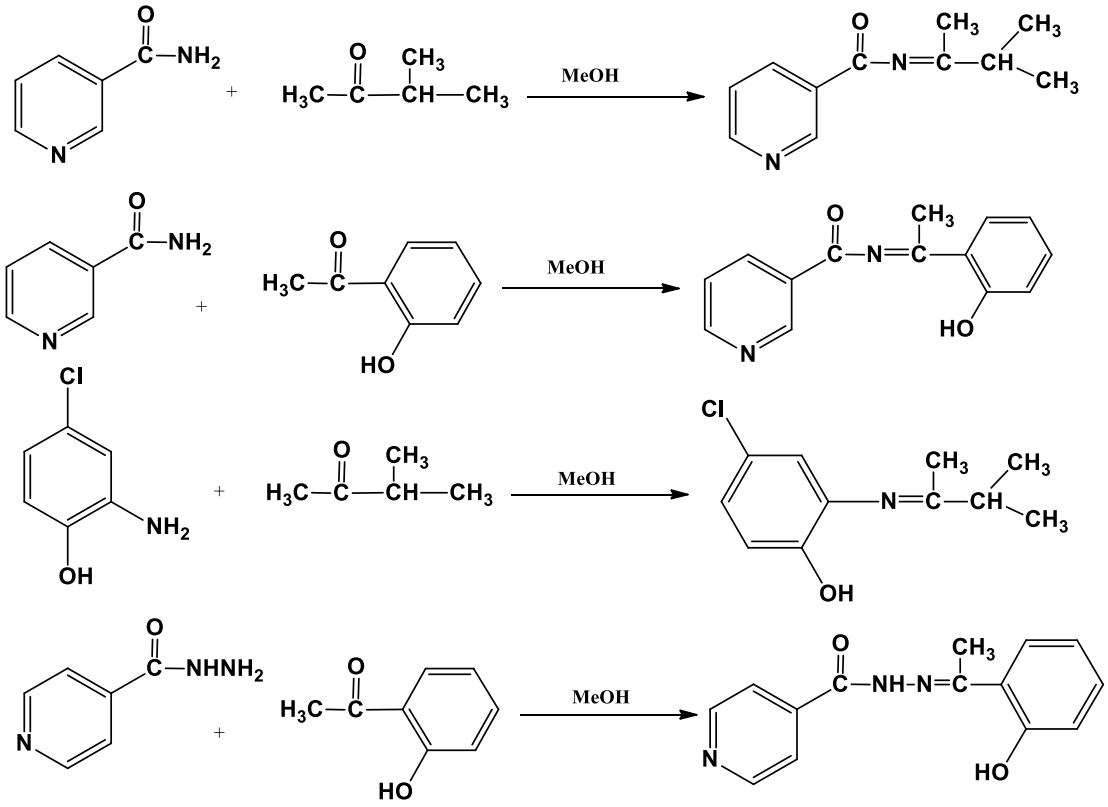
In 2008, several azomethines were synthesized from 2-amino thiazolyl bromocoumarin and a variety of aldehydes by conventional heating, refluxing, and MW irradiation in ethanol solvent by Venugopala KN, Jayashree BS [10]. They noticed that the MWI method is more efficient than conventional heating and refluxing because products were obtained in 1-2 min in the MWI method compared to the very long time taken (1-2 hrs) for getting the same product in the other two methods. In addition, antibacterial screening of formed compounds was also carried out by Venugopala *et al*.



Scheme 7. Synthesis of azomethines byVenugopala *et al*.

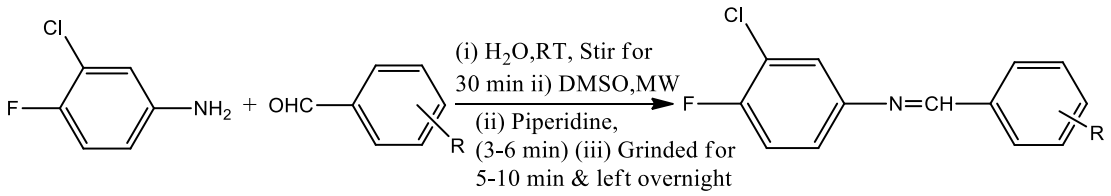
The synthesis of new bidentate or tridentate Schiff bases was formed by condensing methylisobutylketone with nicotinamide/2-amino-4-chlorophenol and 2-hydroxyacetophenone with nicotinamide/isoniazide by Mishra AP *et al*. [39] in the year 2008. These Schiff bases were then used by them to synthesize complexes with VO(II) and Co(II). Both Schiff bases

and their complexes were analyzed for antimicrobial activities by them. They found that complexes show higher antimicrobial activities than ligands.



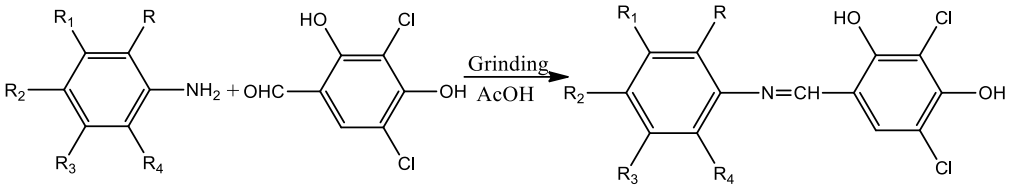
Scheme 8. Synthesis of azomethines by Mishra AP *et al.*

Different methods for the formation of azomethines by using 3-chloro-4-fluoroaniline and several benzaldehydes were reported by Naqvi A. *et al*. [40] in the year 2009. They run reactions at room temperature in a water medium, under MW irradiations in DMSO solvent, and by grindstone technique. All of these methodologies were green, but out of these, the water-based formation of azomethines was the best on the yield, followed by the MW assisted method, which was considered better than the friction-activated method. The MW-assisted method was considered best by Naqvi A *et al*. based on time.



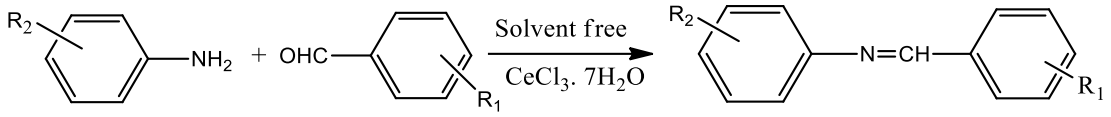
Scheme 9. Synthesis of azomethines by Naqvi A *et al.*

Vibhute AY *et al*. [41] documented a simple & efficient way for the formation of some new azomethines with the use of 3,5-dichloro-2,4-dihydroxy benzaldehyde and substituted aniline in the solvent ethanol containing traces of glacial acetic acid by grindstone technique in the year 2009. The researchers obtained all the compounds in a short duration of 15-20 min. The researchers also produced the same compounds by heating the same components for 3 hours, but the yield, in that case, was quite poor.



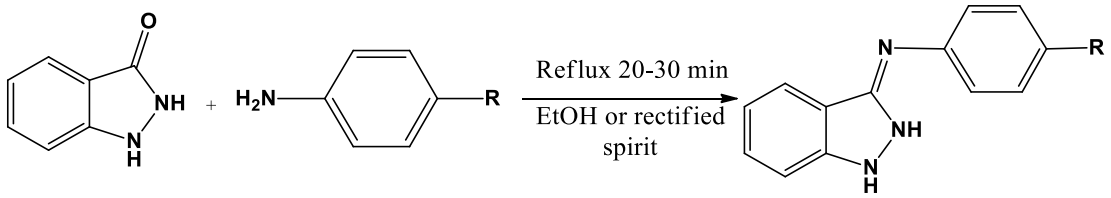
Scheme 10. Grindstone-assisted synthesis of azomethines by Vibhute AY *et al*.

Preparation of azomethines by reaction of primary aromatic amines with aryl aldehydes catalyzed by cerium chloride heptahydrate without using solvent was registered by Ravishankara L.*et al*. [42] in the year 2010. First, they performed reactions in the absence of catalyst. They noted that in the absence of catalyst, the deactivated amines either did not give any reaction or provided a very poor yield of product similarly deactivated aldehydes, i.e., aldehydes bearing electron releasing groups provide product at a faster rate in the presence of catalyst than in the absence of a catalyst.



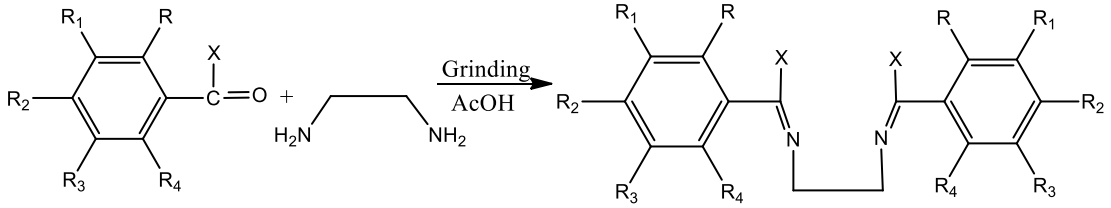
Scheme 11. Cerium chloride heptahydrate catalyzed synthesis of azomethines by Ravishankar L. *et al*.

Muthumani P, Meera R. *et al*. [43] prepared a series of azomethines by the reaction of 3-indazolone and 4-substituted aniline by heating the solution in a water bath using a reflux condenser in the year 2010. The scientists also screened the formed compounds for biological activities like antibacterial, anti-inflammatory, and analgesic.



Scheme 12. Synthesis of azomethines by Muthumani P *et al*.

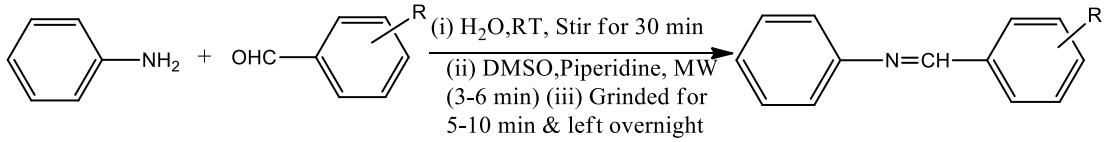
The synthesis of novel bis-azomethines from aromatic aldehydes/ketones and ethane-1,2-diamine under different reaction conditions like (a) Grindstone, acetic acid, (b) refluxing with ethanol in the acetic acid catalyst was documented by Chavan SB *et al*. [44] in the year 2010. In the grindstone technique, the product was produced in 1-10 min, whereas under refluxing, 2-15 min were taken. Secondly, a lot of wastage of solvent occurred in the refluxing method. So it was concluded by the researchers that friction activated method was superior to the conventional method as no solvent was used in this method; hence it was in accordance with protocols of green chemistry.



Scheme 13. Synthesis of azomethines by Chavan SB *et al*.

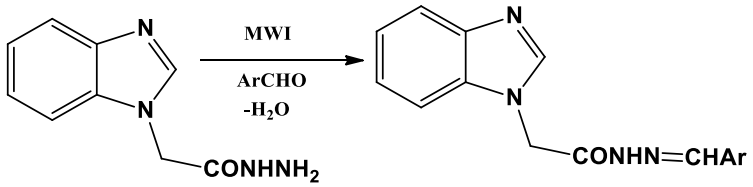
Khadsan RE, *et al*. [45] developed different greener methodologies in the year 2010 for the formation of azomethines by using benzaldehyde and aniline bearing different substituents under different conditions like (a) by stirring with water at room temperature (b) by irradiating

a mixture in MW in the presence of DMSO solvent and piperidine catalyst (c) by grinding mixture in the absence of catalyst and solvent. Researchers summed up that formation of azomethines in water at RT was best. However, the time taken was more than MWI method because in the MWI technique solvent and catalyst used were not safe, and also the yield was not as good as in the former method despite of eco-friendly source of energy and grindstone method for synthesis of azomethines provided a product in low yield by taking a long time. However, no solvent or catalyst was applied.

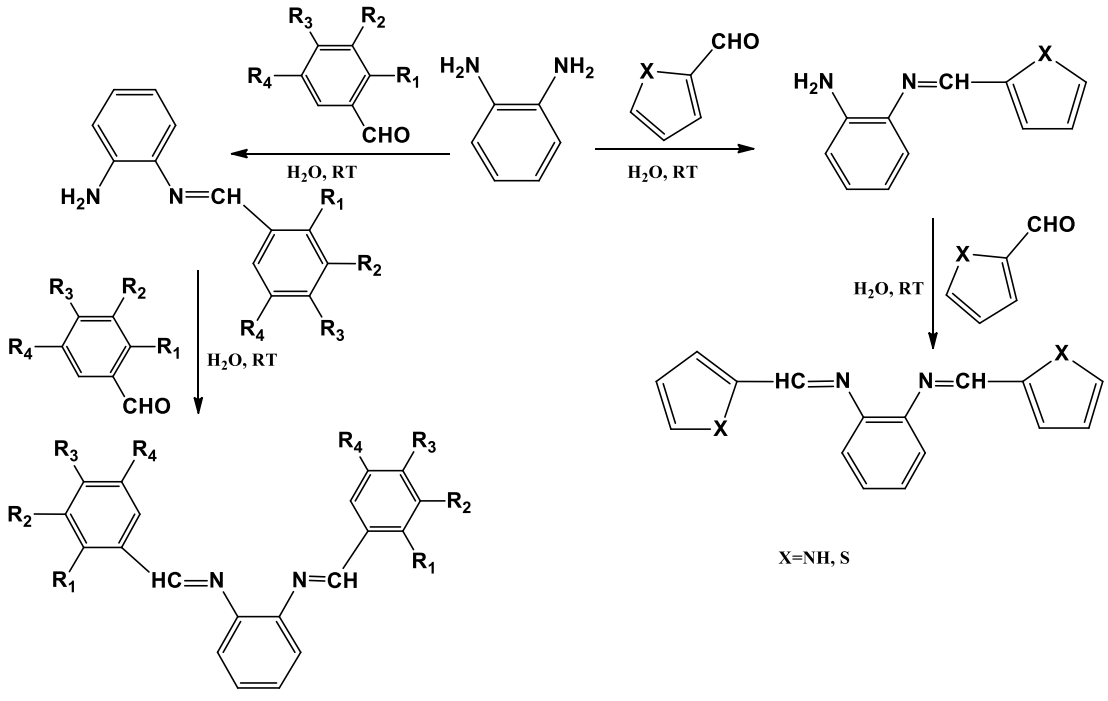


Scheme 14. Synthesis of azomethines by Khadsan RE *et al.*

In the year 2010, microwave-assisted green method for the formation of Schiff bases was reported Somani R *et al*. [46]. Reactions were performed between the ethanolic solution of 2-(2-Methyl-1H-benzimidazol-1-yl)-acetohydrazide and various aromatic aldehydes in the presence of catalyst glacial acetic acid by the researchers, for this purpose reaction mixture, was refluxed under microwave for 30-40 minutes by them. All the azomethines prepared were pure and screened for antibacterial activity against *P. aeruginosa*, *S. typhii*, *S. aureus*, and *E. coli*.



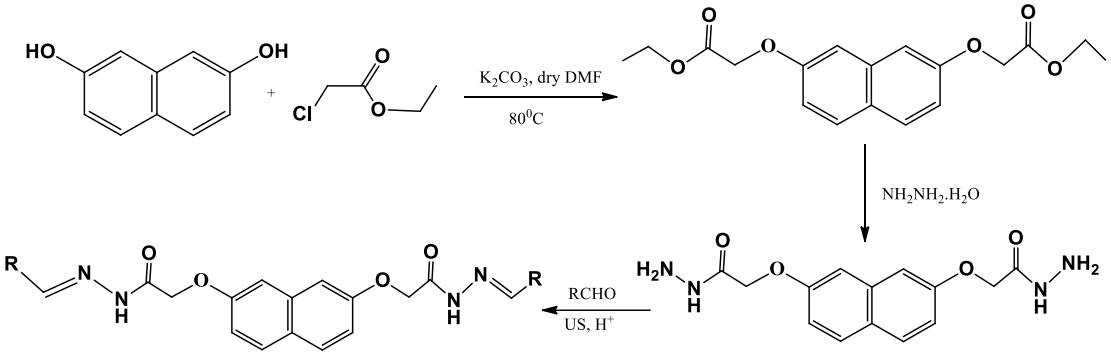
Scheme 15. MWI synthesis of azomethinesSomani R *et al.*



Scheme 16. Synthesis of azomethines by Rao VK *et al.*

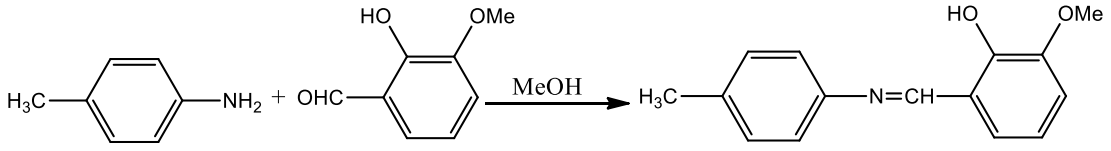
A novel and ecofriendly approach for forming Schiff bases was given by Rao VK *et al*. [47] in the year 2010 by condensing 1,2-diaminobenzene with various aromatic aldehydes in the aqueous medium. Various spectroscopic techniques characterized all the Schiff bases prepared by researchers. VK Rao *et al*. also synthesized the same compounds by conventional methods using NaOH as a catalyst in ethanol solvent. Still, they found that azomethines formed by using water as a solvent are cost-effective and safe.

A library of azomethines was synthesized by Satyanarayana VSV *et al*. [48] by condensing 2-substituted acetohydrazide and different aldehydes by refluxing with $CHCl_3$, CH_3OH, AcOH medium, and acetic acid medium under ultrasonic conditions in the year 2011. They saw that the ultrasound method was much better than refluxing because, under the US irradiations, reactions proceeded at a faster rate and took only 6-12 min; on the other hand, reactions were preceded at a slower pace and took 180-240 min. Hence ultrasound was considered a much more effective and energy-conservative method.



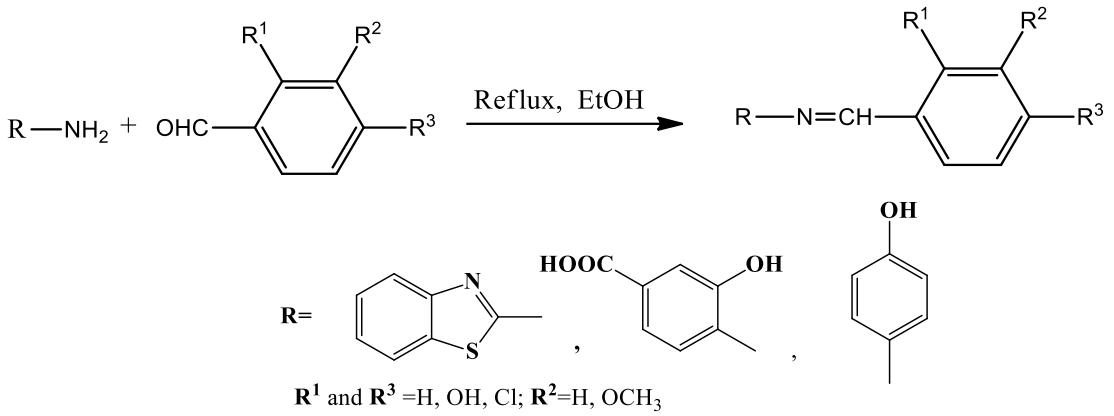
Scheme 17. Synthesis of azomethines by Satyanarayana VSV *et al*.

Bendale AR. *et al*. [49] reported different methodologies for the formation of azomethinesin the year 2011. Reactions were carried out in UV chamber, sonicator, and by grinding technique. First, solvent-free and catalyst-free synthesis of azomethines with the use of a UV chamber was documented by them, and after this, they prepared azomethines with an acetic acid catalyst with the use of a sonicator. They also performed reactions in methanol solvent without the application of a catalyst. The researchers also synthesized the same azomethines without the aid of solvent and catalyst by the grindstone method. They concluded that azomethines were synthesized in a very short time when reactions were carried out with a catalyst in a sonicator.



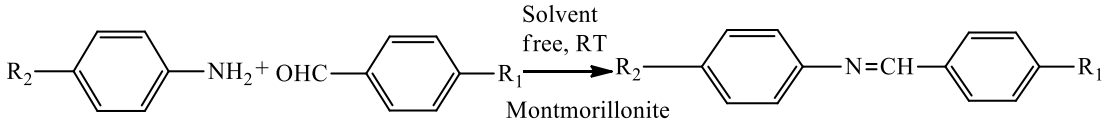
Scheme 18. Synthesis of azomethines by Bendale AR *et al*.

Muhammad AA, *et al*. [50], in the year 2011, synthesized three new series of azomethines by condensation of a variety of aldehydes and amines in 25 ml ethanol by refluxing for 2 hrs. The azomethines so obtained were screened by the researchers for antibacterial and antifungal activities. Antibacterial activities were tested on *E. coli, S. aureus and B. subtilis*, and antifungal activities were tested on *Aspergillus niger* and *Chalara Corda* by Muhammad AA *et al*..



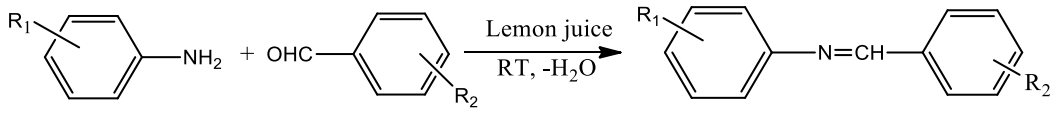
Scheme 19. Synthesis of azomethines by Muhammad AA *et al.*

Solventless formation of Schiff Bases by using Montmorillonite as a Heterogeneous Catalyst was reported by Hossein N *et al*. [51] in the year 2012. They first grind the reactants and the catalytic amount of montmorillonite, then put this reaction mixture into the flask and stir it mechanically for a suitable time. After the reaction was completed, the researchers added chloroform to the reaction concoction. They saw that reactions were much faster with aldehydes than with ketones.



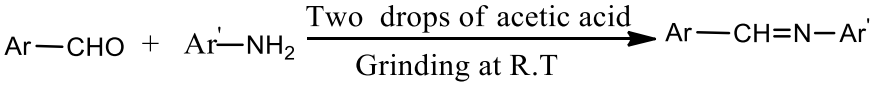
Scheme 20. Synthesis of azomethines by Hossein N *et al.*

In 2012, Green synthesis for the formation of azomethines in good yields by the reaction between primary aromatic amines and aryl aldehydes at room temperature under solvent-free conditions by employing lemon juice as natural acid catalyst was revealed Patil *et al*. [52]. The researchers prepared a large number of azomethines by taking a variety of aldehydes and amines. It was observed by Patil *et al*. that most of the reactions took 0.25-5 hours for completion, and in a few cases, no product was obtained even after quite a long time. No doubt their approach to synthesizing azomethines was green, but the time taken was long.



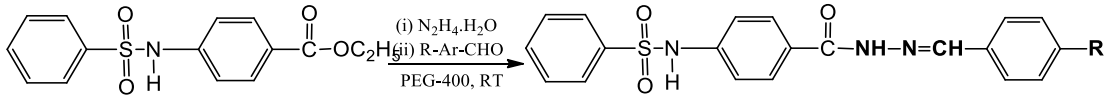
Scheme 21. Lemon juice catalyzed the synthesis of azomethines by Patil *et al.*

Acetic acid-catalyzed synthesis of azomethines at room temperature under solvent-free conditions by grinding together indole-3-aldehyde with substituted aryl amines was reported by Subhash BJ *et al*. [53] in the year 2012. They prepared a series of imines by using heterocyclic aldehydes and highly substituted aromatic amines, and then this method was compared with the conventional method. In the end, Subhash BJ *et al*. concluded that the grinding method (6-12 min and 83-91% yield) is superior to the conventional method (60-210 min and 63-73% yield) in terms of both time and yield of products.



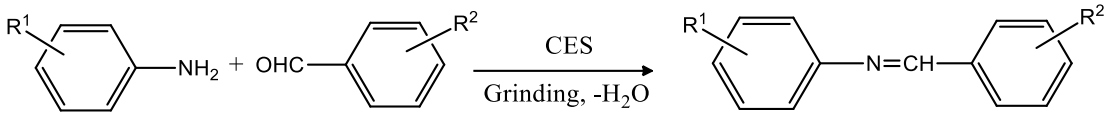
Scheme 22. Acetic acid-catalyzed synthesis of azomethines by Subhash BJ *et al.*

In 2012, PEG-400 as a green reaction medium, was used to synthesize azomethines in an efficient and eco-friendly way without using catalysts by Jagrut VB *et al*. [54]. For the preparation of azomethine, the reactants were dissolvedinPEG-400. They were stirred for 10 hrs by Jagrut VB *et al*. PEG retained its activity and recovered from the used reaction medium. It was noticed that though PEG served as a green reaction medium, reactions take a long time to complete.



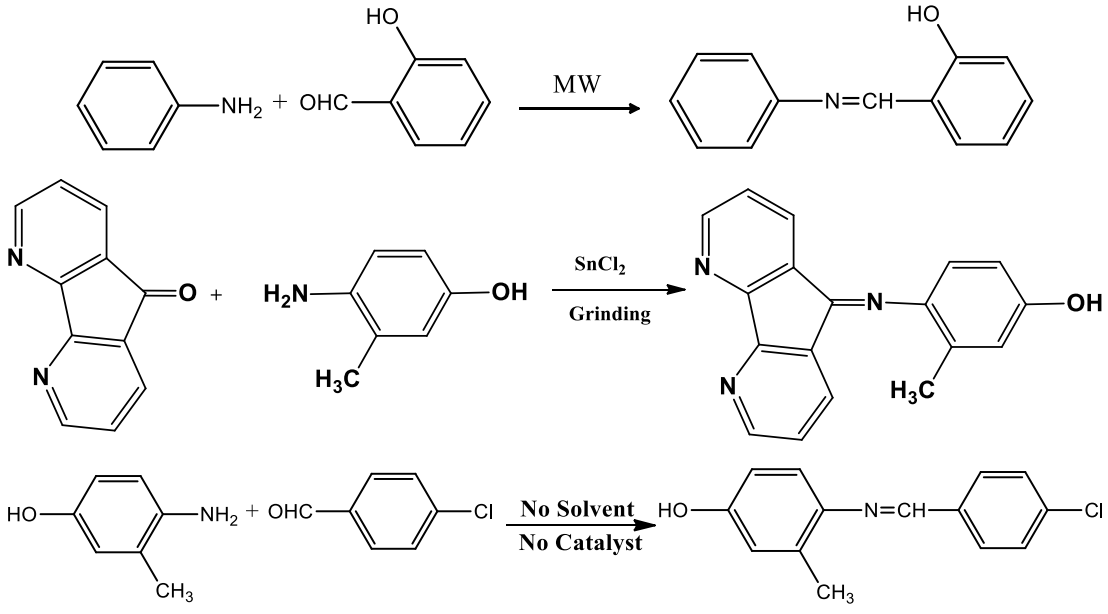
Scheme 23. PEG-400 catalyzed synthesis of azomethines by Jagrut VB *et al*.

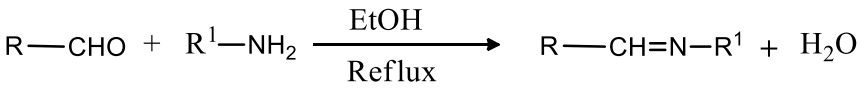
An innovative Green approach for the formation of Schiff bases by using CES as a natural catalyst under solvent-free conditions was developed by Patil *et al*. [55] in the year 2012. By this approach, the researchers prepared a series of imines by grinding together aromatic aldehyde, substituting aromatic amine and calcined egg shells (CES). They obtained all the azomethines in good yield in a short time.



Scheme 24. CES catalyzed the synthesis of azomethines by Patil *et al*.

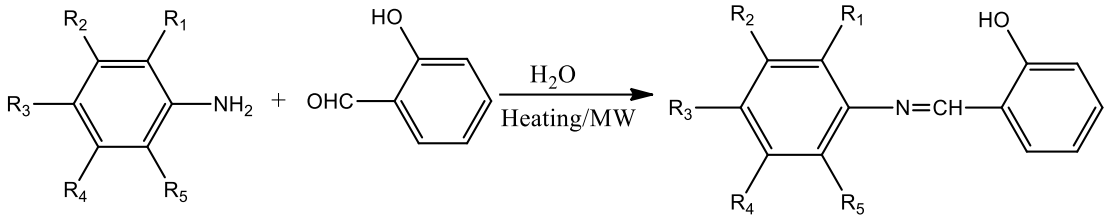
NK Chaudhary [56] reported the formation of Schiff bases by carrying out the reaction between aldehydes and different aryl amines by applying different conditions like (a) MW, Solvent and catalyst-free (b) Grinding, $SnCl_2$, Solvent-free (c) Grinding, Solvent, and catalyst-free (d) Reflux, EtOH or MeOH, acidic/basic or neutral medium in the year 2013. Then various methodologies were compared by them. He found that solventless synthesis by microwave irradiation is the most efficient based on time and cost. Different azomethines prepared by him were screened for biological activities and used for preparing complexes with transition metal ions.





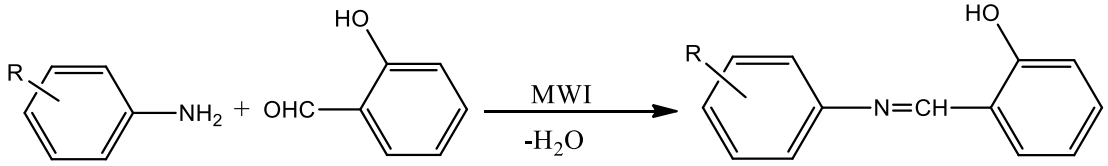
Scheme 25. Synthesis of azomethines by NK Chaudhary.

The preparation of azomethines was carried out under microwave irradiation by reaction of 2-hydroxybenzaldehyde with several aryl amines in water by Bhagat S, Sharma, N [57] in the year 2013. To set suitable reaction conditions, reactions were performed at different temperatures by the researchers by keeping the power of the MW reactor constant. The most suitable temperature detected by them was 70°C as the maximum yield was obtained at this temperature, so they performed other reactions at this temperature. Yield and reaction time was compared with conventional methods by them. In the end, researchers concluded that the MWI method was much more efficient than the conventional method.



Scheme 26: Synthesis of azomethines by Bhagat S, Sharma, N.

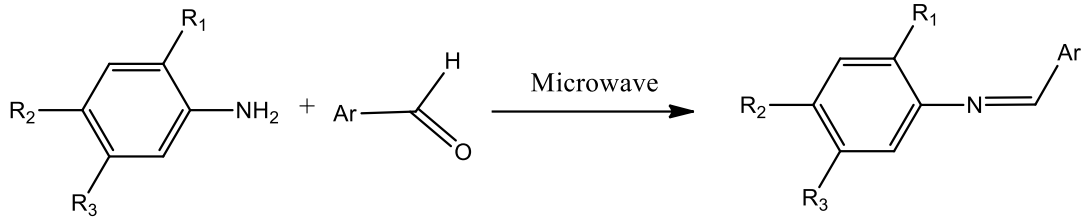
In 2014, microwave-assisted synthesis of Schiff Base under solvent-free conditions was documented by Abirami M *et al*. [58]. A long series of azomethines was prepared by reaction of 2-Hydroxyaldehyde and a variety of aromatic amines in 3-5 min by Abirami M *et al*. All the azomethines were obtained in excellent yield. The approach was made completely green by using environmentally safe and harmless materials by the researchers.



Scheme 27. MW assisted synthesis of azomethines by Abirami M *et al.*

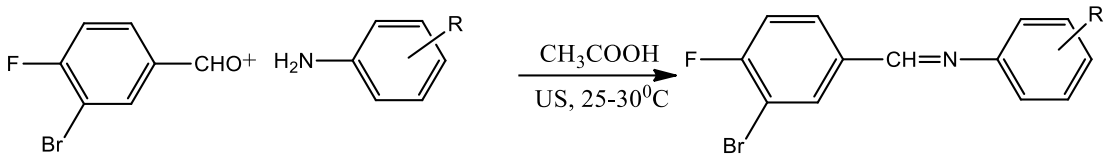
In 2014, microwave-assisted ecofriendly formation of some substituted azomethines was reported by Bodale VP *et al*. [59]. The approach was made quite green by them as a source of energy that is MW irradiations was eco-friendly, but at the same time, DMSO, a toxic non-green solvent, was used in excessive amounts. No doubt it was seen by them that yield of azomethines was excellent.

Solventless synthesis of some imine derivatives assisted by microwave irradiations was given by Bekdemir Y *et al.* [60] in the year 2014. Different powers of MW with and without wetting agent β- ethoxyethanol were used by the researchers to perform reactions, and finally, the inference was drawn by them that at 360 W power of MW reactor in the presence of wetting agent β-EE, the amount of azomethine obtained was maximum and time taken was minimum. All the other reactions were then carried out under this set of conditions with different aldehydes and amines, and as a result, a long chain of azomethines was synthesized. In the end, it was inferred that the MWI method was much more efficient than the conventional method.



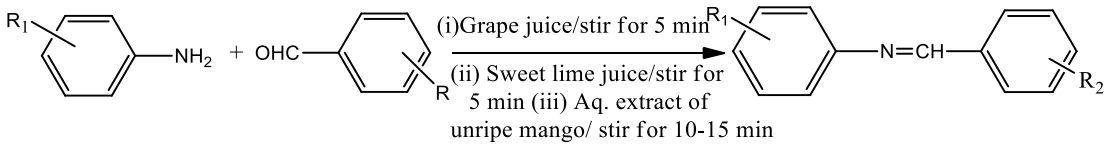
Scheme 28. MW assisted synthesis of azomethines by Bekdemir Y *et al.*

Ultrasound-assisted synthesis of Schiff bases of some 4-nitroaniline/ 2,4-dinitroaniline/3,4-dichloroaniline/4-methoxy-3-nitro aniline with 3-bromo-4-fluoro-benzaldehyde in ethanol solvent and acetic acid as catalyst was done by Santhi N *et al*. [61] efficiently and cleanly in the year 2014. The Schiff bases obtained were characterized by various spectroscopic methods and screened for antibacterial and antimicrobial activities.



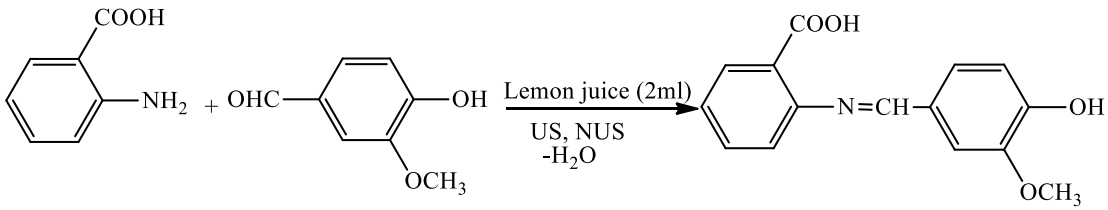
Scheme 29. US-assisted synthesis of azomethines by Santhi N *et al.*

The application of natural acid catalysts like fruit juice of grapes, unripe mango, and sweet lemon to synthesize azomethines under solvent-free conditions was reported by researchers Yadav G, Mani JV [62] in the year 2015. They noted that the yield of azomethines was influenced by the amount of catalyst and found that the product yield decreased by increasing the amount of catalyst. In the end, a conclusion was drawn by Yadav G *et al*. that out of these catalysts, grape juice was found to be best as it provided maximum yield, and sweet lime juice provided minimum yield.



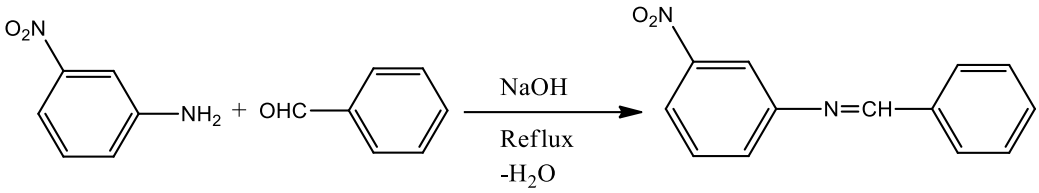
Scheme 30. Synthesis of azomethines by Yadav G, Mani JV.

In the year 2015, The prime synthesis of azomethines by performing a reaction of 4-hydroxy-3-methoxybenzaldehyde and 2-amino benzoic acid (Anthranilic acid) under conventional/nonultrasonic (NUS) by refluxing and ultrasonic conditions with a catalytic amount of lemon juice as a green acid was given by Mohammed A *et al*. [63]. It was seen by them that reactions under ultrasonic conditions proceeded more rapidly (10 min) than under NUS conditions (1 hr). The scientists also compared morphological data, % yield, and stability of azomethines formed in two methods. It was inferred by the scientists that under ultrasonic conditions, compounds formed were relatively more stable and crystalline in nature.



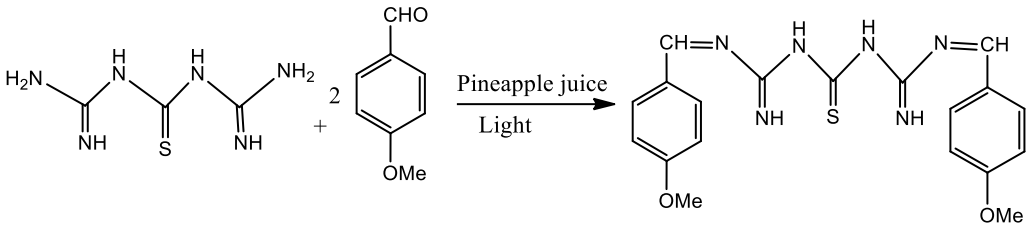
Scheme 31. Lemon juice catalyzed the synthesis of azomethines by Mohammed A *et al.*

Muzammil K *et al*. [64] synthesized azomethines by refluxing an alcoholic solution of m-nitroaniline and benzaldehyde along with 2-3 drops of NaOH in the year 2015. After this, researchers used these azomethines as ligands to form complexes with metals copper and cobalt. The antimicrobial activities of these complexes were screened by Muzammil K *et al*. They further said that copper complexes possess more antimicrobial activity than cobalt complexes.



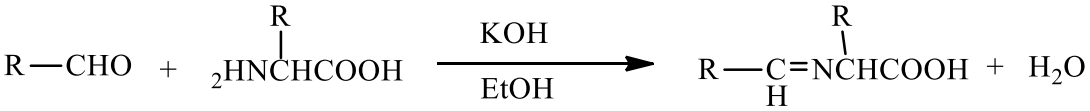
Scheme 32. Synthesis of azomethines byMuzammil K *et al*.

In 2016, visible light-assisted synthesis of azomethines catalyzed by pineapple juice by the reaction of 1,3-diformamidinothiocarbamide and various aldehydes was documented by Tayade DT, Ingole SP [65]. The scientists took reactants and 20 ml of fresh pineapple juice to perform the reaction in a round bottom flask. After exposure of the reaction mixture to sunlight for 52 hrs, the product was obtained in good yield. They also synthesized some other azomethines in the same way but by adding a drop of sulphuric acid.



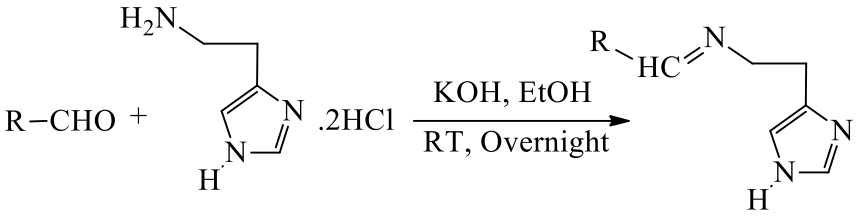
Scheme 33. Synthesis of N'(p-methoxy)benzylene-N''-(p-methoxy)benzylene-iminothiobiurate.

KOH catalyzed synthesis of some azomethines derived from some aldehydes with amino acids such as glycine and alanine in EtOH solvent was reported by Mohana, ER [66] in the year 2016. *In silico* studies of synthesized compounds were also analyzed by them. The biological properties of obtained azomethines were predicted by the researchers by the application of PASS software.



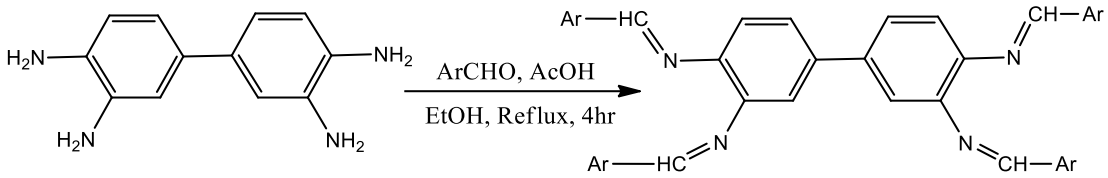
Scheme 34. Synthesis of azomethines from amino acids by Mohana, ER.

KOH catalyzed synthesis of a large number of histamine Schiff bases in the presence of dry MeOH as solvent at RT by the reaction of histamine with a variety of aldehydes was documented by Akocak S *et al*. [67] in the year 2017. It was examined by the researchers that the activity of histamine Schiff bases depends upon the structure of aldehyde used for the preparation of Schiff bases. They further said that these azomethines act as activators for five selected human (h) CA isozymes, the cytosolic hCA I, hCA II, and hCA VII, the membrane-anchored hCA IV, and transmembrane hCA IX.



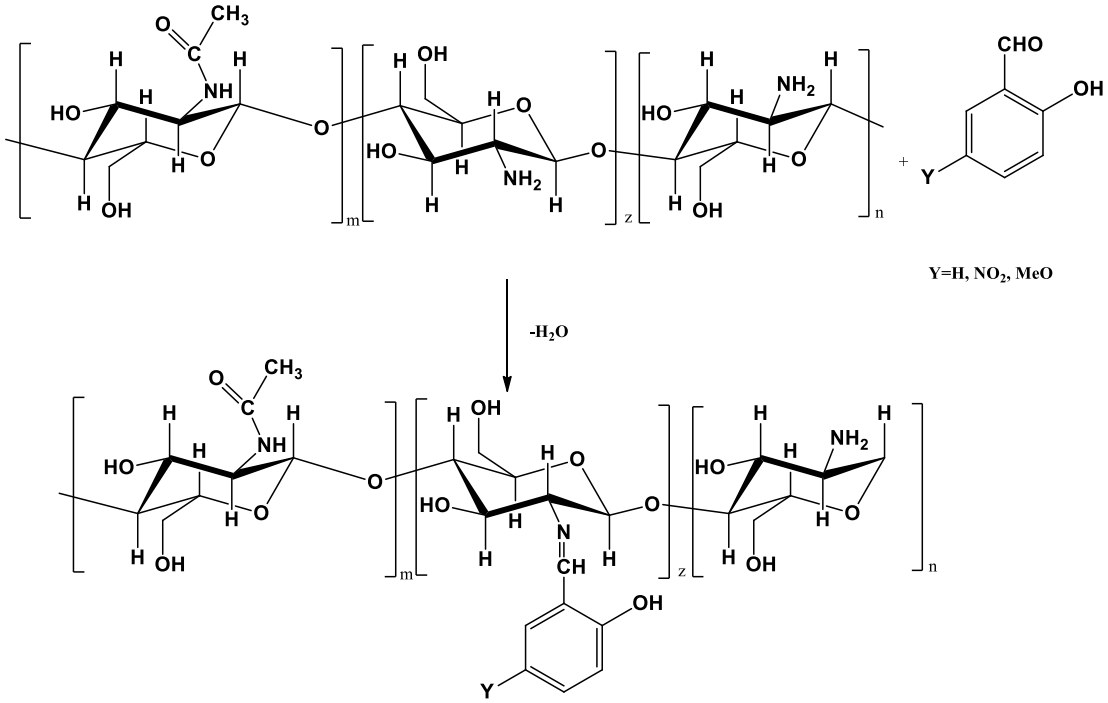
Scheme 35. Synthesis of azomethines from histamine by Akocak S *et al.*

In the year 2017, a series of three new tetra Schiff bases were prepared by condensation of biphenyl-3,3′,4,4′-tetraamine and three different aromatic aldehydes (in excess 4 mol equivalent) dissolved in ethanol solvent in the presence of acetic acid as catalyst under reflux (4 hrs) was reported by Ahmed DS *et al*. [68]. These azomethines so formed were applied as photostabilizer for PVC by them. They further noted that azomethine formed from salicylaldehyde showed maximum photo-stabilization activity for PVC films, whereas azomethine prepared by using 4-nitrobenzaldehyde showed minimum photo-stabilization activity for PVC films.



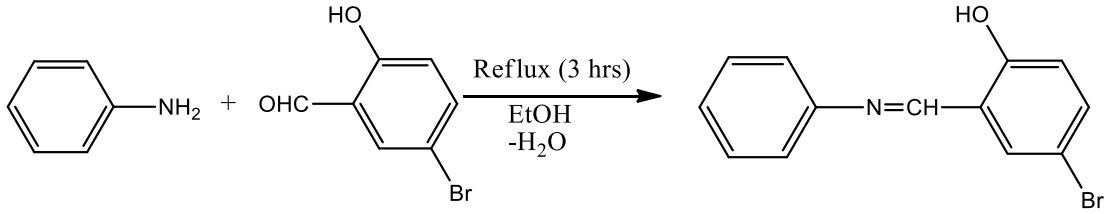
Scheme 36. AcOH catalyzed synthesis of azomethines by Ahmed DS *et al.*

The biopolymericAzomethines were prepared by reaction of Chitosan and Salicylaldehydes by Barbosa HFG *et al.* [69] in the year 2017. The azomethines so formed by Barbosa *et al*. were used as ligands to form complexes with Pt(II) and Pd(II). Complexes formed by researchers were screened for antimicrobial and antitumor activities. They found that the antitumor activity of these complexes of chitosan-based biopolymericazomethines was very good against the breast cancer cell line MCF-7.



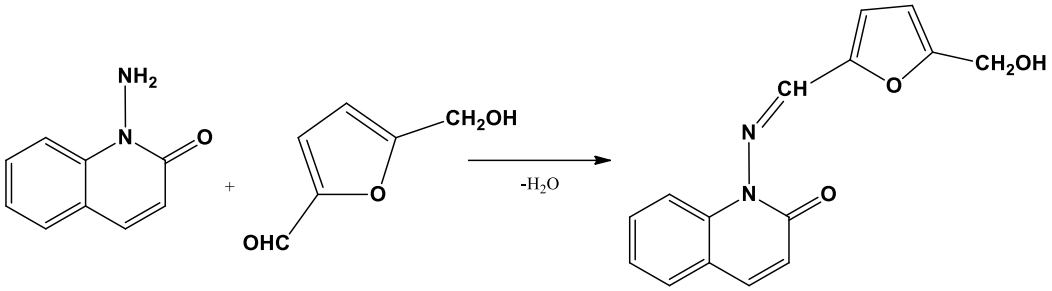
Scheme 37. Synthesis of biopolymeric azomethines by Barbosa HFG *et al.*

The preparation of azomethine by refluxing a mixture of 5-Bromo-2-hydroxybenzaldehyde and aniline in super dry ethanol for 3 hours was given by Dave RH *et al*. [70] in the year 2018. Complexes of this ligand with metals Cu(II), Ni(II), Co(II), Mn(II), V(II), and Fe(II) were also formed by the researchers. The researchers screened both complexes and ligands for antibacterial activity against several bacteria like *E. coli, B. subtilis*. They said that the antibacterial activity of complexes is superior to azomethines.



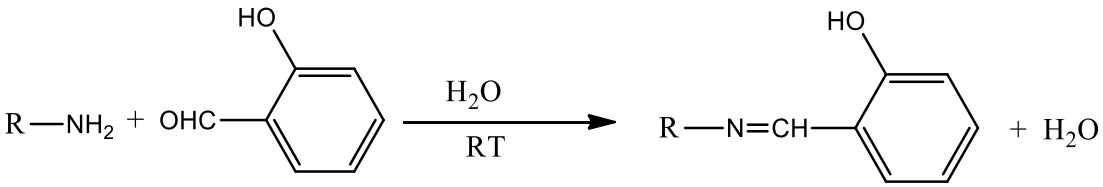
Scheme 38. Catalyst-free synthesis of azomethines by Dave RH *et al*.

In 2018, The formation of azomethine by refluxing 5-hydroxy methylfuran-2-carbaldehyde and 1-aminoquinolin-2(1H)-one in ethanol solvent was given by Alturiqi *et al* [71]. Complexes of this ligand with several different metal ions like Cr(III), Ru(III), Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) were also synthesized by Alturiqi *et al* . All the synthesized compounds were tested for cytotoxic activities against human breast (MCF-7) and lung cancer (A549) cell lines.



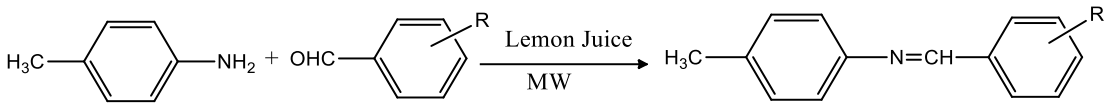
Scheme 39. Synthesis of azomethines by Alturiqi *et al*.

In 2018, Shamly P et al. [72] gave a new synthetic approach for the formation of salicylaldimines in an aqueous medium. The researchers prepared three different azomethines by reacting 2-hydroxybenzaldehyde with aniline, ethylenediamine, and aminobenzoic acid. The scientists prepared and tested the complexes of these azomethines with the metal Ni and Mg for antimicrobial properties. A comparison of antimicrobial properties among these complexes and with azomethines was also executed by Shamly P et al.. They said that the antimicrobial properties of metal complexes were better than azomethines, and among metal complexes, antimicrobial activity was higher for Mg metal complexes. They also used these complexes for the purification of water, as these kill microorganisms.



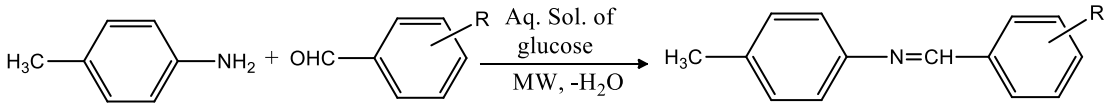
Scheme 40. Water-based synthesis of azomethines by Shamly P *et al*.

MW-assisted green synthesis of azomethines in lemon juice medium was reported by Bedi *et al*. [73] in 2018. The researchers performed a series of reactions by taking an equal amount of aromatic aldehydes and p-toluidine and using lemon juice as ecofriendly, economical, biodegradable and green reaction medium. The azomethines were prepared in a very short duration of time and were characterized by various spectroscopic techniques by Bedi *et al*..



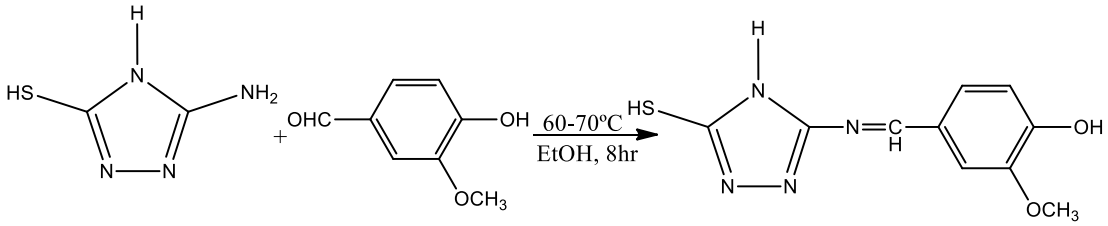
Scheme 41. Lemon juice catalyzed the synthesis of azomethines under MW irradiations by Bedi *et al.*

In 2018, a series of azomethines was prepared by Bedi *et al*. [74] by condensing aromatic aldehydes and p-toluidine. They reported the synthesis in an aqueous medium by using glucose as a green catalyst under an eco-friendly source of energy, i.e., MW irradiations. The azomethines synthesized by them were of high purity, and the yield was quite excellent.



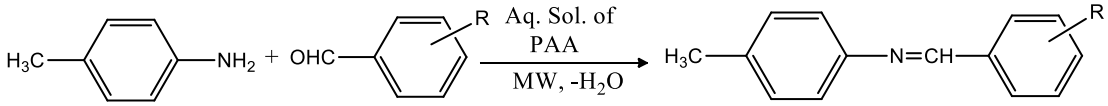
Scheme 42. Glucose catalyzed synthesis of azomethines under MW irradiations by Bedi *et al.*

In the year 2019, acid-catalyzed formation of azomethine by refluxing an ethanolic solution of 5-amino-4*H*-1,2,4-triazole-3-thiol and 3-hydroxy-4-methoxybenzaldehyde for 6 hours was documented by Vinusha HM *et al*. [75]. The synthesized azomethines were utilized as a ligand by the researchers to form complexes with Cu(II), Co(II), Mn(II), Ni(II), and Zn(II) metal ions. *In vitro* antibacterial activity of azomethine and their complexes were assessed by Vinusha HM *et al*. against nine food pathogens. They noticed that metal complexes of azomethines exhibited higher antibacterial effects than the azomethines themselves. Antioxidant activities and *in vitro* Inhibitory effects on yeast α-glucosidase were also studied by them. They concluded that the potentiality of the Zn complex was highest among the complexes tested for antibacterial, antioxidant, and inhibitory activity.



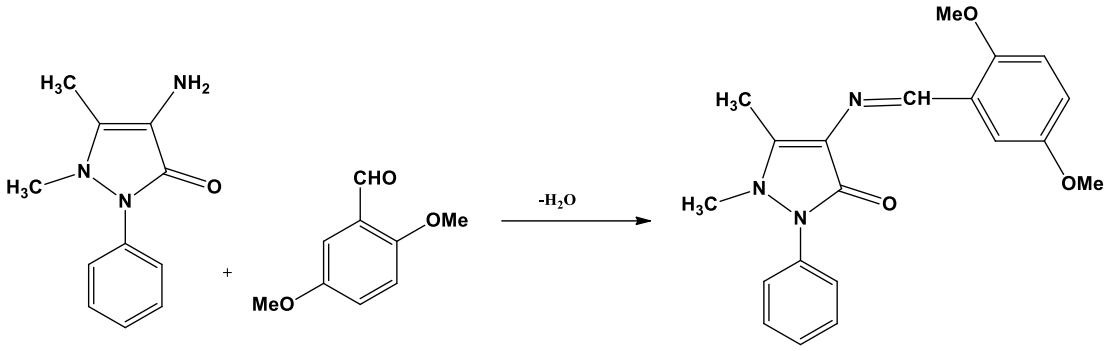
Scheme 43. Synthesis of azomethines by Vinusha HM *et al.*

A long chain of azomethines was prepared by performing reactions between p-toluidine and different aromatic aldehydes by Bedi *et al*. [76] in the year 2019 by employing polyacrylic acid as a biodegradable catalyst. All the reactions were carried out under MW irradiations as a green source of energy. All the azomethines the researchers obtained were pure and in good yield.



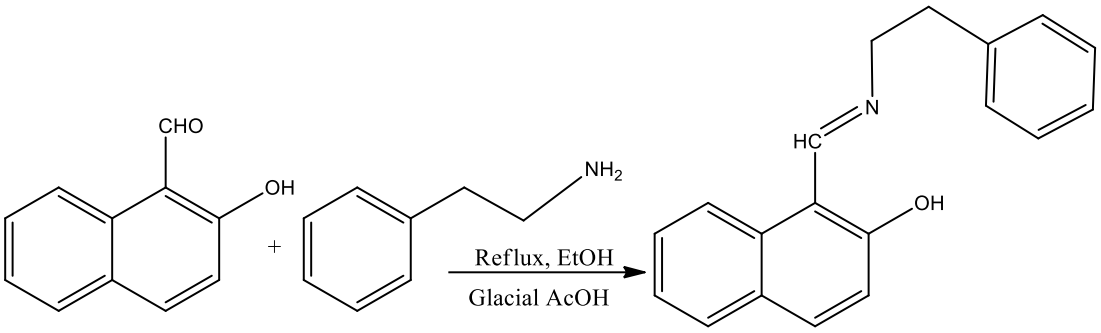
Scheme 44. PAA catalyzed the synthesis of azomethines by Bedi *et al.*

In the year 2019, MW assisted the preparation of an azomethine by condensation of 2,4-dimethoxybenzaldehyde and 4-Amino-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one was given by A-Zoubi W *et al*. [77]. The azomethine so synthesized was used as a ligand to form complexes with Ni(II), Pd(II), Pt(IV), Zn(II), Cd(II), and Hg(II) metal ions by them. The scientists screened both azomethine and its complexes for antibacterial and antifungal activities against S. aureus, E. coli, C. albicans, and C. tropicalis.



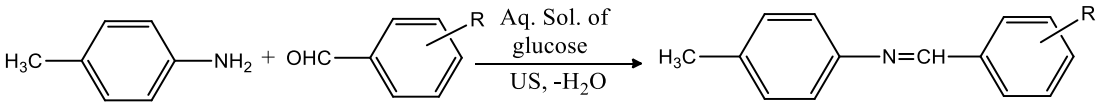
Scheme 45. MW assisted preparation of an azomethine by A-Zoubi W *et al.*

A new Schiff base was formed by Hatim IH *et al*. [78] in 2019 by reacting phenylethylamine with a hot ethanolic solution of 2-hydroxynaphthaldehyde in the presence of glacial acetic acid. Then the synthesized compounds were checked for toxicity by the scientists. After examining the toxicity of the compounds, they said that compounds were almost safe for the environment as well as for humankind.



Scheme 46. Synthesis of 1-((phenethylimido)methyl)naphthalen-2-ol by Hatim IH *et al*.

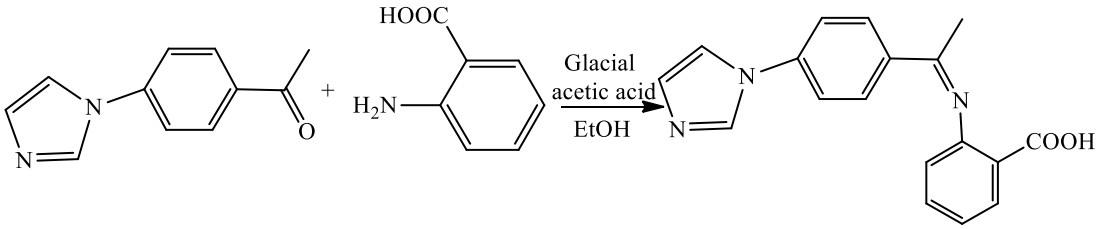
Bedi *et al*. [79] reported US-assisted green synthesis of azomethine in 2019 by carrying out a reaction between various aromatic aldehydes and p-toluidine by using glucose as an eco-friendly catalyst in a water medium. The researchers prepared the azomethines in a very short time, and they were purified by recrystallization. Characterization of azomethines formed was done by IR, NMR, and mass spectroscopy.



Scheme 47. US assisted synthesis of azomethines by using glucose catalyst in water medium by Bedi *et al.*

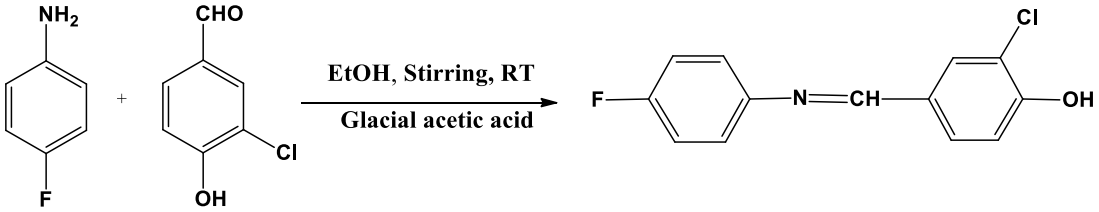
Glacial acetic acid catalyzed the formation of azomethine by condensation of Antharanilic acid (dissolved in ethanol), and Imdazoleacetophenone (dissolved in absolute hot ethanol) was reported by Hussein TI *et al*. [80] in the year 2020. The reactions of synthesized azomethine were performed by the scientists with Ni(II), Cd(II), and Co(II) metal ions to obtain the requisite complexes. Screening of *in vitro* antimicrobial activities of both the azomethine

as well as its metal complexes was done by the researchers. They noticed that complexes show much higher antimicrobial activity than azomethine.



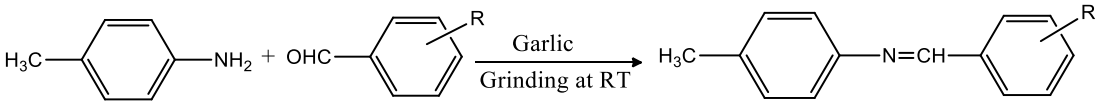
Scheme 48. Synthesis of azomethines by Hussein TI *et al.*

In 2020, A systematic and convenient synthetic approach for the construction of azomethine from 5-chlorosalicylaldehyde and 4-fluoroaniline at room temperature in EtOH solvent was documented by Ommenya FK *et al*. [81]. They performed the reaction by adding two drops (0.2 mL) of glacial acetic acid. After this, metal complexes were prepared by the scientists by the application of this azomethine. Testing of both azomethine and its metal complexes for their bactericidal activity against no. of gram-positive and gram-negative bacteria was done by Ommenya FK *et al*. It was concluded by them that as compared to free ligand metal complexes possess higher antibacterial activity.



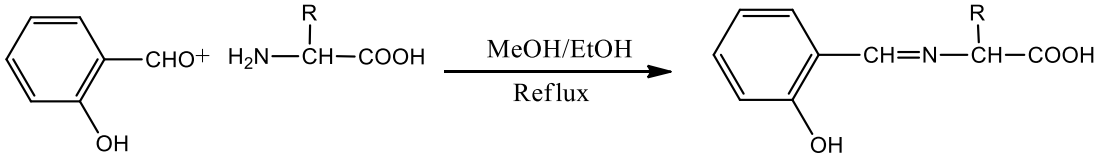
Scheme 49. Glacial acetic acid-catalyzed synthesis of azomethines by Ommenya FK *et al*.

In the year 2020, garlic acid-catalyzed synthesis of azomethines by grinding together aromatic aldehydes and p-toluidine was reported by Bedi P *et al*. [82]. The synthesized azomethines were purified by recrystallization with ethyl alcohol, and purified compounds were characterized by various spectroscopic techniques like IR, NMR, and mass.



Scheme 50. Garlic catalyzed synthesis of azomethines by Bedi *et al.*

A series of six Schiff bases were prepared by refluxing a mixture of salicylaldehyde and various amino acids in methanol solvent for 12 hours in 2020 by Fattuoni C *et al*. [83]. The Schiff bases so formed were characterized by IR and NMR spectroscopic techniques. They also did the examination of antiproliferative and DNA-binding activity. The aqueous solution of synthesized azomethines was also used by Fattouni C to determine the protonation constant.



Scheme 51. Synthesis of azomethines from amino acids by Fattouni C *et al.*

Table 1. Various Reaction conditions, catalysts, and solvents for the synthesis of Azomethines.

S.NO.	Reference	Catalyst	Solvent	Reaction conditions
1	2	------	EtOH	Reflux (2 Hrs)
2	34	Neutral Al_2O_3	DCM	MW (4 min)
		------	C_6H_6	Reflux (over 7 Hrs)
		Anhydrous $MgSO_4$	DCM	RT (Stir 2 Hrs)
3	35	P_2O_5/Al_2O_3	-----	RT (Stir 25-120 min)
4	36	CaO	-----	MW(70 sec)
5	37	------	EtOH	US (10-20 min)
6	38	SiO_2	EtOH	US (10 min)
7	10	------	EtOH	Reflux (2 Hrs)
		------	-------	Heat (in oil bath at 180°C)
			EtOH	MW(65-113 sec)
8	39	------	Water	RT (Stir 30 min)
		Piperidine	DMSO	MW(3-6 min)
		-----	------	GS(overnight)
9	40	CH_3COOH	-----	GS (15-20 min)
10	41	$CeCl_3.7H_2O$	-----	Reflux(5-50min)
11	42	------	Rectified spirit or EtOH	Reflux(20-30min)
12	43	Glacial CH_3COOH	$CHCl_3$- MeOH	Reflux(3-4Hrs)
			DMSO	US(6-12 min)
13	44	------	Water	RT(stir 30 min)
		Piperidine	DMSO	MW(3-6 min)
		------	------	GS(overnight)
14	45	------	Water	Stir (RT)
15	46	Glacial CH_3COOH	EtOH	MWI, reflux (30-40 min)
16	47	NaOH	EtOH	Reflux (2 hrs)
		------	Water	RT (Stir 10 min)
17	48	CH_3COOH	------	GS(1-10 min)
			EtOH	Reflux (2-15min)
18	49	------	-------	UV Chamber (15min)
		------	MeOH	US (45°C, 13-15min)
		CH_3COOH	MeOH	US (45°C, 9-10min)
		-----	-----	GS (Overnight)
19	50	-----	EtOH	Reflux (2 Hrs)
20	51	Montmorillonite	------	Grind(RT 3-120 min)
21	52	Lemon juice	Lemon juice	RT(15-300min)
22	53	CH_3COOH	------	Grind (2-3 min)
23	54		PEG-400	RT(stir 10 Hrs)
24	55	CES	------	Grind (10-15 min)
25	56	------	------	MW
		$SnCl_2$	------	Grinding (RT)
		------	------	Grinding
		------	EtOH/ MeOH	Reflux
26	57	------	Water	RT (Stir 1-2 Hrs)
			Water	MW (0.5-2 min)
27	58	------	-----	MW (3-5 min)
28	59	------	DMSO	MW(40-62 sec)
29	60	β-ethoxyethanol	------	MW (1-3min)
		-------	EtOH	Reflux (120min)
30	61	CH_3COOH	EtOH	US (25-30°C)

S.NO.	Reference	Catalyst	Solvent	Reaction conditions
31	62	Grape juice[a], sweet lime juice[b], unripe mango[c]	------ [a,b] Water [c]	RT (stir 5-10 min)[a,b] RT(stir10-15 min)[c]
32	63	Lemon juice	Lemon juice	Reflux (1Hr)
				US(10 min)
33	64	NaOH	EtOH	Reflux (4 Hrs)
34	65	Pineapple juice	Pineapple juice	Sunlight (52 Hrs)
35	66	KOH	EtOH	Heat (60-180 min)
36	67	KOH	MeOH	RT
37	68	CH_3COOH	EtOH	Reflux (4Hrs)
38	69	------	EtOH+ Glacial acetic acid	Thermostated bath (55°C), stir 18 Hrs
39	70	------	EtOH	Reflux (3Hrs)
40	71	------	EtOH	Reflux (3Hrs)
41	72	------	Water	Stir at RT (10 min)
42	73	Lemon Juice	Lemon Juice	MW (0.5-3 min)
43	74	Glucose	Water	MW (0.5-4 min)
44	75	Acidic medium	EtOH	Reflux (6Hrs)
45	76	Polyacrylic Acid	Water	MW(0.5-1.5 min)
46	77	------	------	MW(15 min)
47	78	Glacial acetic acid	EtOH	Reflux (3Hrs)
48	79	Glucose	Water	US
49	80	Glacial acetic acid	EtOH	Reflux (2Hrs)
50	81	Glacial acetic acid	EtOH	RT
51	82	Garlic	------	GS
52	83	------	EtOH/MeOH	Reflux (12Hrs)

Recently some new methods for forming azomethines and their respective complexes with various metal ions have been developed by researchers in the years 2021 and 2022. In a few of these synthetic strategies, Schiff bases were synthesized without the use of catalyst [84-92], and in others, some toxic and biodegradable catalysts like Et_3N, piperidine, HCl, egg white, ascorbic acid, $NaHCO_3$, acetic acid have been employed [93-100].

3. Conclusions

The present review describes various synthetic routes of azomethines reported in current literature with an update of recent research findings. This review shows that there is much scope for the researcher to change the reaction condition, change the catalyst, modify the catalyst, or even develop various novel methodologies. Apart from all these, azomethines obtained by following different methodologies can be tailored to novel pharmacore as per need.

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Conflicts of Interest

The authors declare no conflict of interest.

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